Amendments to the Specification

Please replace the following paragraphs with the rewritten paragraphs below.

[0003] Description of the Related Art: *In vitro* membrane diffusion systems with automated sampling are widely available for flow-through diffusion cells. However, applicants are presently aware of only two commercial systems that provide both static diffusion cells and automated sampling. Hanson Research Corp. of Chatsworth, CA, sells the Hanson MicroettePlus™ Transdermal Diffusion System, and Logan Instruments Corp. of Somerset, VT, sells the Logan System-902 and Logan System-912 Automated Transdermal Sampling Systems. Logan also plans to sell[[s]] an upgraded system that includes a cell design similar to the 902-system and an XYZ robot for automatic sampling. Although, the diffusion systems available from Hanson Research and Logan Instruments exhibit differences in design, the systems available from both companies includes a large amount of small diameter tubing and pumps (peristaltic or syringe) that move fluids through multiple compartments within the systems.

[0005] As illustrated in FIG. [[2]]4, in the Hanson MicroettePlus™ Transdermal Diffusion System, the diffusion cell consists of a single chamber, but the input arm of the receptor chamber is connected by tubing to a syringe chamber (Microette unit) and the output arm to a central sample collection chamber. Samples from the receptor chambers are collected in the central sample collection chamber by positive displacement initiated by the syringe unit. Therefore, the MicroettePlus™ Transdermal Diffusion System also utilizes multiple chambers interconnected by tubing.

Under the section entitled "BRIEF DESCRIPTION OF THE DRAWINGS", please insert the two paragraphs below, between paragraphs **[00011]** and **[00012]**:

FIG 2 provides a schematic illustration of twelve sampling ports of a Logan System-902 Transdermal Sampling System.

FIG 3 provides a schematic illustration of six diffusion cells and bubble traps of Logan System-902 Transdermal Sampling System.

[00012] FIG. [[2]]4 provides a schematic illustration of the Hanson MicroettePlus™ Transdermal Diffusion System.

[00013] FIG. [[3]]5 provides a schematic illustration of a diffusion cell according to the present invention, wherein the sampling arm and bubble trap are part of the receptor compartment.

[00014] FIG. [[4]]6 provides a schematic illustration of a diffusion cell according to the present invention, wherein the first opening of the receptor compartment is positioned on the side of the cell, preventing accumulation of air bubbles under the diffusion membrane.

[00015] FIG. [[5]]7 provides a schematic illustration of a diffusion cell according to the present invention, wherein the first opening creates a diffusion area that is tilted upward toward the second opening, which works to prevent accumulation of air bubbles under the diffusion membrane

[00016] FIG. [[6]]8 ~~and FIG. 7~~ provides schematic illustrations of diffusion cells according to the present invention, wherein the diffusion cells include a ~~top section and a bottom section and the bottom section can be removed and made of different sizes to~~sampling port and provide receptor compartments of ~~different~~smaller volumes.

[00017] FIG. [[8]]9 provides a schematic illustration of an alternative embodiment of a diffusion cell according to the present invention that includes a top section and a bottom section. The bottom section can be removed and made of different sizes to provide receptor compartments of different volumes.

[00018] FIG. [[9]]10 provides a schematic illustration of a bubble channel that can be formed between the first opening and the second opening in the receptor compartment of a diffusion cell according to the present invention.

[00019] FIG. [[10]]11 depicts one example of arranging the static diffusion cells in a mounting apparatus, wherein the sampling ports are lined up in multiple parallel rows.

[00020] FIG. [[11]]12 depicts another example of arranging the static diffusion cells in a mounting apparatus, wherein the sampling ports are lined up in a single row.

[00021] FIG. [[12]]13 depicts sampling heads to match a mounting apparatus as illustrated in Figures 10 and 11, respectively.

[00022] FIG. [[13]]14 illustrates a ~~reinforcing ring for use with a diffusion membrane in a diffusion cell of the present invention.~~completed sample disc, which includes a cover fabric, a patch system, a membrane and a thin plastic donut ring that defines the diffusion area.

[00027] A first embodiment of the diffusion cell of the present invention is illustrated in FIG. [[3]]5. The diffusion cell of the present invention includes a single-chamber receptor compartment, a donor compartment, a diffusion membrane, and a sampling arm. As can be seen in FIG. [[3]]5, the diffusion membrane is positioned over the first outlet and once the diffusion cell is assembled, a top surface of the diffusion membrane forms at least a portion of the bottom surface of the donor compartment, and a bottom surface of the diffusion membrane forms at least a portion of the top surface of the receptor compartment. The diffusion membrane used in a diffusion cell according to the present invention may be any natural or synthetic material suitable for application in a diffusion cell. Natural membranes useful in a diffusion cell according to the present invention include, but are not limited to, skin, mucosal membranes, cornea, and epithelial membranes (e.g., intestinal, colonic, or nasal epithelial membranes). In a preferred embodiment, the diffusion membrane is formed of animal or human skin.

[00028] In order to ensure the diffusion membrane is properly held in place between the donor and receptor compartments, the diffusion membrane may be positioned over or disposed between a device or component that reinforces the diffusion membrane and allows the diffusion membrane to be securely held in place without undesired damage to the membrane. As is illustrated in FIG. [[13]]14, in preferred embodiments, a reinforcing ring, such as a washer or gasket, is positioned under the diffusion membrane or over the diffusion membrane. Alternatively, two reinforcing rings may be positioned both over and under the diffusion membrane. A reinforcing ring used in a diffusion cell of the present invention can be formed of any suitable material, such as a polymer material. In addition, a cover material, such as a cover fabric (shown in FIG. [[13]]14), can be positioned over the diffusion membrane and test material.

[00031] The first outlet may be formed to any size and shape that allows positioning of the diffusion membrane over the first opening. For example, where the receptor compartment is designed to accommodate a 5-30 ml volume of receptor medium, the first opening is preferably sized from about 0.7 to about 5 cm^2. However, the size and shape of the first opening can be varied, as desired, to allow the use of differently sized diffusion membranes and to suit any particular test conditions. As can be seen in FIG. [[3]]5, the first opening can also be adapted to facilitate positioning of the diffusion membrane and association of the donor compartment with the receptor compartment. The first outlet and donor compartment of the diffusion cell illustrated in FIG. [[3]]5, are designed with a flange that facilitate clamping of the donor compartment over the diffusion membrane and the first opening of the receptor compartment. Of course, it is to be understood that the donor compartment can be associated with the receptor compartment using any suitable mechanism, not just a clamp. For example, the donor compartment can be associated with the receptor compartment using a threaded connection, a male-female connection, a snap-fit connection, or through a friction or interference fit. Both the donor compartment and the receptor compartment, including the first opening, can be adapted as necessary to facilitate the use of a desired mechanism for the association of the donor compartment with the receptor compartment.

[00035] ~~FIG. 4,~~ FIG. [[5]]6 and FIG. [[8]]7 illustrate embodiments of the diffusion cell of the present invention that facilitate the automatic migration of bubbles from the underside of the diffusion membrane positioned at the first outlet of the receptor compartment to the bubble trap formed at the second outlet of the receptor compartment. These designs permit bubbles that may be formed near the diffusion membrane to move towards the bubble trap formed by the second outlet without requiring removal of the diffusion cell from a diffusion apparatus or manipulation of the diffusion cell by a human operator (*e.g.*, tilting the diffusion cell to move bubbles into the bubble trap).

[00036] As shown in FIG. [[4]]6, the first outlet of the receptor compartment can be positioned on a side of the receptor compartment instead of the top. Designing the diffusion cell in this manner effectively rotates the arrangement of the diffusion membrane from a roughly horizontal position to a roughly vertical position. Because the diffusion membrane is positioned horizontally on one side of the receptor compartment, any bubbles formed within the receptor compartment will tend to rise away from the surface of the diffusion membrane to the top of the receptor compartment, where the second outlet and bubble trap are located. In addition, if desired, the top surface of the receptor chamber can form an incline that raises toward the second outlet, thereby further increasing the likelihood that any bubbles formed within the receptor compartment will automatically migrate into the bubble trap formed by the second outlet. Where the first outlet is positioned at one side of the diffusion cell, it is necessary that the association of the diffusion membrane, donor compartment and receptor compartment form a seal that prevents leaking of the receptor medium from within the receptor compartment. Any suitable mechanism for associating the donor and receptor compartments can be used. The necessary seal at the interface between the diffusion membrane, donor compartment and receptor compartment can be formed solely by the mechanism associating the components, or, alternatively, one or more additional sealing members may be included to provide the desired seal. The mechanisms already described for associating the donor compartment and receptor compartment, as well as the additional sealing members described

herein are also suitable for use in a diffusion cell designed according to the embodiment illustrated in FIG. [[4]]6.

[00037] FIG. [[5]]7 ~~and FIG. 8~~ illustrates diffusion cells according to the present invention wherein both the first and second outlets of the receptor compartment are located at the top of the receptor compartment, but the first outlet is designed such that the portion of the top surface of the receptor compartment formed by the bottom surface of the diffusion membrane inclines upward toward the second outlet. This tilt or inclination of the top surface of the receptor compartment toward the second outlet of the receptor compartment works to automatically direct any bubbles that form or come to rest on the bottom surface of the diffusion membrane toward the bubble trap formed by the second outlet.

[00038] In a particularly preferred embodiment, the diffusion cell of the present invention is not only designed with receptor compartment having a top surface that inclines upward toward the second opening, but the diffusion cell also includes a channel connecting the first and second outlets. The channel can simply be a depression formed in the top surface of the receptor compartment that extends between the first and second outlets. An illustration of such a channel is provided in FIG. [[9]]8. Typically, the first outlet of the receptor compartment will not be designed such that the bottom surface of the diffusion membrane is flush with the other portions of the top surface of the receptor compartment. Because of this, bubbles may be trapped at the step formed where the bottom surface of the diffusion membrane interfaces with the remainder of the top surface of the receptor compartment. Forming a channel between the first and second outlet reduces any step formed at this interface and thereby further facilitates the automatic migration of bubbles from the bottom surface of the diffusion membrane to the bubble trap formed by the second outlet.

[00040] To better facilitate tailoring the volume of the receptor compartment to a chosen diffusion study, the diffusion cell of the present invention can be designed having separable top and bottom sections (shown in FIG. [[6]]9 ~~—FIG.8~~). The top section of such an embodiment is formed as a cap or a plug, includes the first outlet of the receptor compartment and integrates

an area for association of the donor compartment with the receptor compartment. A bottom surface of the top section also forms at least a portion of the top surface of the receptor compartment. Preferably, the top section also incorporates the second outlet of the receptor compartment and, as a result, the sample arm and bubble trap of the diffusion cell. The bottom section is typically a cup-, well-, or tube-shaped reservoir that is removable from the top section of the diffusion cell. The shape or geometry of the bottom section is preferably designed for efficient stirring of the receptor medium. A sealed receptor compartment of a given volume is formed when the top and bottom sections of the diffusion cell are properly associated. By varying the volume of the bottom section of a diffusion cell having separable top and bottom sections, the volume of the receptor compartment can be readily tailored to a meet the needs of a desired diffusion study.

[00041] Where the diffusion cell of the present invention is designed with separable top and bottom sections, the two sections of the diffusion cell can be associated using any suitable means. In a preferred embodiment (illustrated in FIG. [[8]]9) the top and bottom section are designed to fit together with a friction or interference fit. In such an embodiment, the top section may include a lip, flange, or other feature that ensures the top section is inserted into the bottom section to a desired depth, providing a receptor compartment having a desired volume. Moreover, to ensure that an adequate seal is formed between the top and bottom sections, the top or bottom section can incorporate one or more sealing members, such as one or more O-rings or gaskets. Where the top and bottom sections of a diffusion cell of the present invention are designed to be associated with a friction or interference fit, the force required to associate and dissociate the top and bottom sections should be at least sufficient to maintain the two sections together during a diffusion test and to form an adequate seal where the top and bottom sections interface.

[00047] Where automatic sampling of multiple diffusion cells is desired, the diffusion sampling system of the present invention can include, for example, a robot with multidirectional flexibility, such as an XYZ. XYZ robots are often used in high throughput screening applications and are capable of controlled, programmable movements in all

directions along the XYZ axes. XYZ robots can also be provided with sampling heads that allow the simultaneous sampling of several cells (generally up to 6 to 12 cells simultaneously). Depending on the positioning of the diffusion cells in the mounting apparatus, different robot sampling heads can be used. Examples of two designs for the blocks and the matching sampling heads are shown in Figs. [[10]]11-12. The static diffusion cells of the present invention are also adapted for manual sampling.